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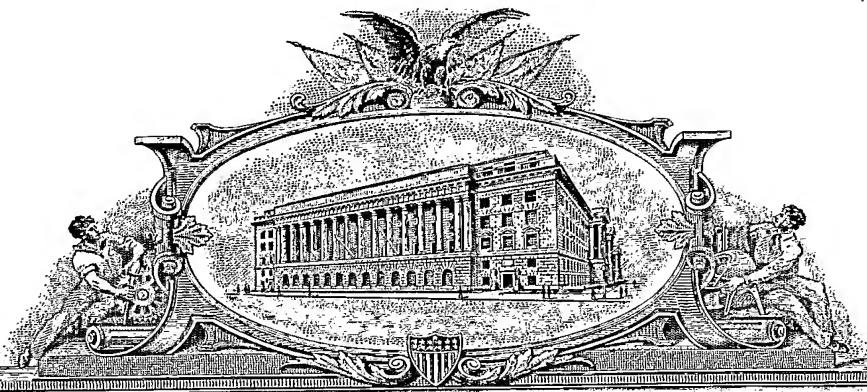
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PROVISIONAL APPLICATION COVER SHEET

Sir:

Transmitted herewith for filing is a **PROVISIONAL** patent application entitled: METHOD FOR PREPARING ADJUSTABLY BIORESORBABLE SOL-GEL DERIVED SiO₂

This provisional application includes:

1. XX A specification (40 pages)
2. XX 4 Sheets of drawings (Figs. 1-7)
3. XX A Credit Card Payment Form in the amount of
____ \$160.00 (large entity) or
XX \$80.00 (small entity).
4. XX This application qualifies for small entity status.

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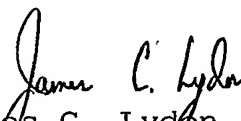
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PROVISIONAL APPLICATION COVER SHEET

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Attorney Docket: **TUR-161**

Please charge any additional required fees or credit any overpayment to our Deposit Account No. 50-1258. Two copies of this Provisional Application Cover Sheet are enclosed herewith.

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METHOD FOR PREPARING ADJUSTABLY BIORESORBABLE SOL-GEL DERIVED SiO_2

FIELD OF THE INVENTION

5 The present invention relates to a method for adjusting the bioresorption rate of sol-gel derived SiO_2 . The present invention further relates to sol-gel derived SiO_2 obtainable with the method.

BACKGROUND OF THE INVENTION

10 The publications and other materials used herein to illuminate the background of the invention, and in particular, cases to provide additional details respecting the practice, are incorporated by reference.

Sol-gel derived SiO_2 is commonly prepared from alkoxides or inorganic silicates that via hydrolysis form a sol that contains either partly hydrolysed silica species or fully hydrolysed silicic acid. Consequent condensation reactions of SiOH containing species lead to formation of larger silica species with increasing
15 amount of siloxane bonds. Furthermore, the species aggregate, form nanosized particles and/or larger aggregates until a gel is formed. The sols derived from alkoxides provide possibilities to adjust the siloxane bond formations and aggregation due to possibility for partial hydrolysis. Reactions (typically at $\leq 40^\circ\text{C}$) are commonly catalysed either by mineral acids (such as HCl and HNO_3)
20 or bases (such as NH_3). The formed gel is then aged (typically at $\leq 40^\circ\text{C}$), dried (typically at $\leq 40^\circ\text{C}$) and/or heat-treated (typically at $\leq 700^\circ\text{C}$) to desired form resulting typically in amorphous and porous SiO_2 . The last step, heat treatment at elevated temperatures ($50\text{--}700^\circ\text{C}$) is typically skipped if the system contains a biologically active agent. The gels that are dried at moderate temperature (at
25 $\leq 50^\circ\text{C}$) are called xerogels (<Gr. xero=dry). Amorphous and porous sol-gel derived SiO_2 is known to be biocompatible and known to dissolve in the living

tissue as well as in solutions simulating the inorganic part of real human body fluid, e.g. in a water solution buffered to pH 7.4 at 37 °C with or without inorganic salts found in real body fluids.

5 The terms used for degradation of a material in or in contact with the living organisms, e.g. living tissue or in contact with plants, microbes etc., are numerous. The terms "biodegradable/biodegradation" are often used as a general definition for degradation in or in contact with living organisms. The terms are also used, especially in connection with carbon-based polymers to describe that the degradation mechanism may include both dissolution in body fluids as well as
10 enzymatic degradation of the polymer matrix. Regarding carbon-based polymers, this often means either decrease in molecular weight or mass loss or both. The terms *bioresorbable/bioresorption* and *bioabsorbable/bioabsorption* are often used to describe materials degradation in or in contact with the living organism, mostly for implanted biomaterials in living tissue describing a degradation mechanism
15 mainly governed by dissolution in the body fluids or by a mechanism that is not exactly known. *Bioresorption* is often used for implantable ceramic biomaterials, such as bioactive glasses or sol-gel derived SiO₂. The general terms *dissolution/soluble* in body fluids are often used for biomaterials implanted into the living tissue. The terms *(bio)erosion/(bio)erodable* are more often in use in drug
20 delivery, especially as it is desirable to distinguish between the mechanisms that control the release. *Surface erosion* describes a material that is so hydrophobic that water absorption does not occur and dissolution/degradation occurs on the surface and bulk erodable material allow water absorption.

25 The importance of bioresorbable materials is growing in controlled release of biologically active agents. It is often desirable to administer drugs as implants or as injected matrices, either in order to achieve local and/or more effective results in a desired tissue or a controlled systemic effect. A large potential group of biologically active agents for this purpose is biotechnologically produced drugs. The number of these drugs is growing fast and it is accelerated by the successful
30 research on the human genome. New biotech drugs are typically larger in size, such as peptides, proteins and polysaccharides, and direct oral administration is

difficult due to intestinal decomposition. In addition, bioresorbable matrices are potential materials for optimising the administration of small molecules by implantation, e.g, to avoid administration several times a day or to optimise the patient docility for drug therapy. In addition, bioresorbable materials are potential
5 matrices as it is desirable to avoid extra removal operations that are commonly done for biostable delivery matrices, (such as PDMS, polydimethylsiloxane). Materials having pore sizes between 1–100 nm are in the same order of magnitude as the size of many peptides and proteins, but solely diffusion-controlled release is often far from the optimal.

10 WO 93/04196 by Zink et al. discloses the idea of encapsulating enzymes in a porous transparent glass, prepared with a sol-gel method. The purpose is to immobilize enzymes in the pore structure and thus, the release of the enzymes is to be avoided. These porous, transparent glasses can be used to prepare sensors for qualitatively and quantitatively detecting both organic and inorganic
15 compounds, which react with the entrapped material. The pore radius in these glasses is so small (under about 4 nm) that the entrapped biologically active materials cannot diffuse out from the glass.

WO96/03117 by Ducheyne et al. discloses controlled release carriers, where biologically active molecules are incorporated within the matrix of a silica-based
20 glass. Here, silica-based glasses are typically multicomponent glasses, and 100 % SiO_2 is a special case, with a very poor dissolution. The release of the biologically active molecules from the carrier is claimed to occur primarily by diffusion through the pore structure and bioresorption is not mentioned to affect the release of biologically active agents.

25 WO 97/45367 by Ahola et al. describes controlled dissolvable silica-xerogels prepared via a sol-gel process. The preparation of dissolvable oxides (silica xerogels) is carried out by simultaneous gelation and evaporation and mainly concerns small particles made by spray-drying or fibres made by drawing. WO 01/13924 by Ahola et al. describes controlled release of a biologically active
30 agent from a sol-gel derived silica xerogel. These inventions provide sustained and/or controlled release delivery devices for biologically active agents, but they

do not give methods for adjusting bioresorption or merely give very limited means for adjusting bioresorption.

WO 00/50349 by Jokinen et al. and WO 01/40556 by Peltola et al. disclose methods for preparation of sol-gel derived silica fibres. WO 00/50349 discloses a method for adjusting the biodegradation rate of the fibres by the controlling the viscosity of the spinning process. WO 01/40556 discloses a method for preparing a bioactive sol-gel derived silica fibre.

WO 02/080977 by Koskinen et al. discloses a method for preparation of a biodegradable silica xerogel comprising infecting and/or transfecting viruses.

10 OBJECTS AND SUMMARY OF THE INVENTION

An object of the present invention is to provide a method for preparing a sol-gel derived SiO_2 with a very fast bioresorption rate.

Another object of the present invention is to provide a method for adjusting the bioresorption rate of sol-gel derived SiO_2 .

15 Still another object of the present invention is to provide a sol-gel derived SiO_2 monolith tailored to have a desired bioresorption rate.

A further object of the present invention is to provide a sol-gel derived SiO_2 coating tailored to have a desired bioresorption rate.

20 A still further object of the present invention is to provide a sol-gel derived SiO_2 particle tailored to have a desired bioresorption rate.

An object of the present invention is to also provide a method for administering a biologically active agent into a human or animal body, or to a plant.

25 Thus the present invention provides a method for preparing a sol-gel derived SiO_2 with a very fast bioresorption rate, said SiO_2 optionally comprising a specific percentage or percentages of a biologically active agent or agents other than the SiO_2 itself with or without protective agent or agents for said biologically active

agent or agents, wherein method a sol-gel derived SiO_2 is prepared from a sol comprising water, an alkoxide or inorganic silicate and a lower alcohol, i.e. an alcohol with ≤ 4 carbons, using a mineral acid or a base as a catalyst, preferably a mineral acid, and said sol is aged and dried. Characteristic for the method is that

5 a) in the sol the starting

- i) pH is from 0.05 to 2.5, preferably 1.5 to 2.5, most preferably 2.0,
- ii) molar ratio of water to the alkoxide or inorganic silicate is 0.5 to 2.5; preferably 1.5 to 2.5,
- iii) molar ratio of alcohol to the alkoxide or inorganic silicate is ≥ 0.5 , preferably ≥ 1.0 ; and

10 b) either,

i) the sol is, without induced changes of sol composition,

- let to gel spontaneously at a temperature of $\leq 25^\circ\text{C}$ or an elevated temperature of 65°C to 90°C , preferably at an elevated temperature of 65°C to 90°C , or

- gelation of the sol is done by forced drying of the sol, or

15 ii) a change or changes of sol composition are induced after sol ageing but before gel formation, said change or changes of sol composition optionally comprising addition of said biologically active agent or agents with or without said protective agent or agents, and

20 the ratio t/t_{gel} is ≥ 0.005 , preferably ≥ 0.1 , most preferably ≥ 0.9 , wherein

t is the ageing time of the sol, i.e. time from preparation of said sol to the induced changes, and

25 t_{gel} is the time point where the sol would have turned to a gel without the induced changes; and

forced drying of the sol is carried out or initiated within a time of ≤ 30 minutes, preferably ≤ 15 minutes, most preferably ≤ 5 minutes, from said induced change or changes.

30 The present invention also provides a method for adjusting the bioresorption rate of sol-gel derived SiO_2 , optionally comprising a specific percentage or percentages

of a biologically active agent or agents other than the SiO_2 itself with or without protective agent or agents for said biologically active agent or agents. Characteristic for the method is that a SiO_2 with the fastest bioresorption rate is obtained according to claim 1; and a SiO_2 with a slower bioresorption rate than the fastest bioresorption rate is obtained by

a) deviating in the sol any of the starting values:

- i) pH,
- ii) molar ratio of water to the alkoxide or inorganic silicate, and/or
- iii) molar ratio of alcohol to the alkoxide or inorganic silicate;

from the values defined in a) i) – iii) of claim 1;

b) carrying out induced changes by addition of a component or components, including optional addition of the biologically active agent or agents with or without said protective agent or agents, said changes affecting any of the values i) – iii) of a) of claim 1 or a) if applied by

- i) not carrying out forced drying, or
- ii) carrying out or initiating forced drying of the sol later than defined in b) ii) of claim 1; and/or

c) deviating the temperature for letting the sol gel spontaneously from the values defined in b) i) of claim 1.

The present invention further provides a sol-gel derived SiO_2 , obtainable according to the method of the invention. Characteristic for the SiO_2 is that

- a) the SiO_2 is a monolith with a minimum diameter of ≥ 0.5 mm,
- b) the SiO_2 comprises no biologically active agent other than the SiO_2 itself.

The present invention still further provides a bioresorbable sol-gel derived SiO_2 , obtainable according to the method of the invention. Characteristic for the SiO_2 is that

- a) the SiO_2 is a monolith with a minimum diameter of ≥ 0.5 mm,
- b) the SiO_2 comprises at least one biologically active agent other than the SiO_2 itself, and

- c) the dissolution rate of the SiO_2 in a TRIS buffer at a temperature of $+37^\circ\text{C}$ and pH 7.4 is $\geq 0.35 \text{ wt-\%/h}$.

The present invention additionally provides a bioresorbable sol-gel derived SiO_2 , obtainable according to the method of the invention to which it is characteristic that

- a) the SiO_2 is a coating with a thickness of $< 0.5 \text{ mm}$,
b) the SiO_2 either comprises no biologically active agent or comprises at least one biologically active agent other than the SiO_2 itself.

The present invention moreover provides a bioresorbable sol-gel derived SiO_2 , obtainable according to the method of the invention to which it is characteristic that

- a) the SiO_2 is a particle with a maximum diameter of $\leq 100 \mu\text{m}$,
b) the SiO_2 comprises no biologically active agent other than the SiO_2 itself, and
c) the dissolution rate of the SiO_2 in TRIS buffer at a temperature of $+37^\circ\text{C}$ and pH 7.4 is $\geq 0.04 \text{ wt-\%/h}$, preferably $\geq 0.07 \text{ wt-\%/h}$ and more preferably $\geq 0.15 \text{ wt-\%/h}$.

The present invention also provides a bioresorbable sol-gel derived SiO_2 , obtainable according to the method of the invention to which it is characteristic that

- a) the SiO_2 is a particle with a maximum diameter of $\leq 100 \mu\text{m}$,
b) the SiO_2 comprises at least one biologically active agent other than the SiO_2 itself, and
c) the dissolution rate of the SiO_2 in TRIS buffer at a temperature of $+37^\circ\text{C}$ and pH 7.4 is $\geq 0.5 \text{ wt-\%/h}$.

The present invention further provides a bioresorbable sol-gel derived SiO_2 , obtainable according to the method of the invention to which it is characteristic that

- a) the SiO_2 is a monolith with a minimum diameter of $\geq 0.5 \text{ mm}$,

- b) the SiO_2 comprises at least one biologically active agent other than the SiO_2 itself, and
- c) the dissolution rate of the SiO_2 in a TRIS buffer at a temperature of +37 °C and pH 7.4 is from 0.001 to 0.06 wt-%/h, preferably from 0.002 to 0.05 wt-%/h, and from 0.006 to 0.025 wt-%/h.

The present invention still further provides a bioresorbable sol-gel derived SiO_2 , obtainable according to the method of the invention to which it is characteristic that

- a) the SiO_2 is a particle with a maximum diameter of $\leq 100 \mu\text{m}$,
- b) the SiO_2 comprises no biologically active agent other than the SiO_2 itself, and
- c) the dissolution rate of the SiO_2 in TRIS buffer at a temperature of +37 °C and pH 7.4 is from 0.001 to 0.008, and preferably from 0.002 to 0.003 wt-%/h.

The present invention also provides a bioresorbable sol-gel derived SiO_2 , obtainable according to the method of the invention to which it is characteristic that

- a) the SiO_2 is a particle with a maximum diameter of $\leq 100 \mu\text{m}$,
- b) the SiO_2 comprises at least one biologically active agent other than the SiO_2 itself, and
- c) the dissolution rate of the SiO_2 in TRIS buffer at a temperature of +37 °C and pH 7.4 is from 0.001 to 0.10 wt-%/h, preferably from 0.002 to 0.07 wt-%/h, and more preferably from 0.006 to 0.05 wt-%/h.

The present invention additionally provides a bioresorbable sol-gel derived SiO_2 , obtainable according to the method of the invention to which it is characteristic that said SiO_2 comprises a biologically active agent other than the SiO_2 itself and said biologically active agent is a peptide, a protein or a cell.

The present invention still further provides a bioresorbable sol-gel derived SiO_2 obtainable according to the method of the invention for administering a biologically

active agent to a human or animal body wherein said use comprises administering selected from the group consisting of oral, buccal, rectal, parenteral, pulmonary, nasal, ocular, intrauterine, vaginal, urethral, topical and transdermal administering.

5 The present invention also provides a method of use of a bioresorbable sol-gel derived SiO_2 monolith, coating or particle according to the invention as defined above for administering a biologically active agent to a human or animal body, wherein said use comprises administering selected from the group consisting of oral, buccal, rectal, parenteral, pulmonary, nasal, ocular, intrauterine, vaginal, urethral, topical, transdermal and surgically implantable administering.

10 The present invention additionally provides a method of use of a bioresorbable sol-gel derived SiO_2 obtainable according to the method of the invention and a bioresorbable sol-gel derived SiO_2 according to the invention for administering a biologically active agent to a plant.

BRIEF DESCRIPTION OF THE DRAWINGS

15 Figure 1 shows dissolution of SiO_2 monolith matrices according to the invention.

Figure 2 shows dissolution of SiO_2 microspheres according to the invention.

Figure 3 shows dissolution of propranolol comprising SiO_2 monolith matrices according to the invention and release of propranolol from the matrices.

20 Figure 4 shows dissolution of propranolol comprising SiO_2 microspheres according to the invention and release of propranolol from the microspheres.

Figure 5 shows dissolution of BSA (protein) comprising SiO_2 monolith matrices according to the invention and release of BSA from the matrices.

Figure 6 shows release of BSA (protein) from SiO_2 monolith matrices according to the invention.

Figure 7 shows release of BSA (protein) from SiO₂ microspheres according to the invention.

DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENTS

Terms

- 5 The term *sol-gel derived SiO₂* refers to a SiO₂ prepared by the sol-gel process wherein the SiO₂ is prepared from a sol comprising SiO₂ that has turned to a gel. Sol-gel derived SiO₂ is typically prepared from alkoxides or inorganic silicates that via hydrolysis form a sol that contains either partly hydrolysed silica species or fully hydrolysed silicic acid. Consequent condensation reactions of SiOH
- 10 containing species lead to formation of larger silica species with increasing amount of siloxane bonds. Furthermore, the species aggregate, form nanosized particles and/or larger aggregates until a gel is formed. In the form of a gel, the solid state dominates, but the system still contains varying amounts of liquids and the material is typically soft and viscoelastic before drying and hard and brittle if it
- 15 is extensively dried. In the form of a sol, liquid state dominates, but the system contains varying amounts of solid phase(s) and the system is still flowing.

- Ageing* of the sol shall be understood to mean that after initial preparation of the sol the sol is let to be (i.e. reactions and/or aggregations go on without induced changes in composition) without spontaneous drying or with simultaneous,
- 20 spontaneous drying in ambient conditions until changes are induced or, if no changes are induced, until it turns to a gel spontaneously. The time from preparation until changes are induced, or if no changes are induced until the sol turns to a gel is referred to as *sol ageing time*. Spontaneous drying typically occurs when the sol is aged so that the system allows evaporation in ambient conditions.
- 25 Optionally, this is prevented by keeping the sol in a closed system.

In the context of this application the phrase *in the sol the starting pH/molar ratio* refers to *pH/molar ratio* at the time when the sol is prepared, i.e. when the original

components of the sol are mixed (excluding those components that are optionally added after ageing of the sol).

In the context of this application the phrase *induced change or changes of sol composition* shall be understood to mean any change intentionally induced to the composition of the sol. It can be a change of composition induced by adding more of one or more of the original components of the sol, e.g. water, the alkoxide or inorganic silicate, the alcohol or the catalyst, i.e. a mineral acid or a base. It can be a change of composition by adding one or more new components to the sol, e.g. a biologically active agent if it changes e.g., the pH of the sol, an acid, base or buffer to adjust the pH, or any other component needed to obtain a desired property of the final SiO₂. It can be a sudden physical change affecting the composition of the sol. Such a physical change can for example be elevation of the temperature or decrease in pressure resulting in a sudden release of volatile components (e.g. water, alcohol, and/or volatile acid or base) of the sol, e.g. sudden forced drying, such as spray drying. Such a physical change could also be subjecting the sol to different forms of energy, e.g. electromagnetic or acoustic energy, which could result in a pronounced change in the composition.

Component or components to be added to induce changes refer to any component added irrespective of whether the component or components are original constituents of the sol or a biologically active agent or agents, or an agent or agents protecting the biologically active agent or agents.

Gel formation shall be understood to mean the time point when the sol turns to a gel, as the solid phase becomes dominant, i.e. the continuous phase, in contrary to that of the sol where the liquid phase dominates. In the form of a gel, the solid state dominates, but the system still contains varying amounts of liquids and the material is typically soft and viscoelastic before drying, and hard and brittle if it is extensively dried. In the form of a sol, the liquid state dominates, but the system contains varying amounts of solid phase(s) and the system is still flowing.

Ageing of the gel should be understood to mean that after gel formation the gel is let to be, either without spontaneous drying or with simultaneous, spontaneous drying.

Biologically active agent in the context of this application refers to any organic or inorganic agent that is biologically active, i.e. it induces a statistically significant biological response in a living tissue, organ or organism. The biologically active agent can be a medicine, peptide, protein, polysaccharide or a polynucleotide. It can be a living or dead cell or tissue, a bacteria, a virus, a bacteriophage and a plasmid or a part thereof. It can be an agent for treatment of diseases in therapeutic areas like alimentary/metabolic, blood and clotting, cardiovascular, dermatological, genitourinary, hormonal, immunological, infection, cancer, musculoskeletal, neurological, parasitic, ophthalmic, respiratory and sensory. It can further be for treatment of diseases like osteoporosis, epilepsy, Parkinson's disease, pain and cognitive dysfunction. It can be an agent for the treatment of hormonal dysfunction diseases or hormonal treatment e.g for contraception, hormonal replacement therapy or treatment with steroidal hormones. It can further be an agent such as an antibiotic or antiviral, anti-inflammatory, neuroprotective, prophylactic vaccine, memory enhancer, analgesic (or analgesic combination), immunosuppressant, antidiabetic or an antiviral. It can be an antiasthmatic, anticonvulsant, antidepressant, antidiabetic, or antineoplastic. It can be an antipsychotic, antispasmodic, anticholinergic, sympathomimetic, antiarrhythmic, antihypertensive, or diuretics. It can be an agent for pain relief or sedation. It can also be a tranquilliser or a drug for cognitive dysfunction. The agent can be in a free acid or base form, a salt or a neutral compound. It can be a peptide, e.g. levodopa; a protein, e.g. a growth factor; or an antibody. It can be a polynucleotide, a soluble ion or a salt.

Protecting agent or agents in the context of this application refer to a substance or substances that are useful for protecting and/or enhancing the biological activity of a biologically active agent.

In the context of this application the term *forced drying* refers to the use of a drying process comprising a sudden physical change that stops or highly slows

down the reactions in the sol leading to the formation of the gel. The physical change can be a change that speeds up the rate of drying; preferably at least momentarily more than ten fold. Such a physical change can for example be pronounced elevation of the temperature or decrease in pressure resulting in a sudden release of volatile components (e.g. water, alcohol, and/or volatile acid or base) of the sol. Such a physical change could also be subjecting the sol to different forms of energy, e.g. electromagnetic or acoustic energy. The physical change can also be an essential decrease of the temperature, preferably freezing the sol, so as to stop or essentially slow down the reactions leading to gel formation. Typically forced drying of the sol is by spray-drying or freeze-drying. *Initiation* of forced drying refers to, e.g. in the case of freeze-drying to freezing of the sol.

The term *dissolution rate* refers to SiO₂ matrix resorption in TRIS (e.g., Trizma pre-set Crystals, Sigma) solution buffered at pH 7.4 and 37 °C that simulates conditions of body fluids. The TRIS solution is from 0.005 M to 0.05 M. In practice the concentration of TRIS solution is varied according to specific demands of the analysis of a biologically active agent since determination of the release rate of the biologically active agent is typically carried out when the dissolution rate of the matrix is determined. It is common that buffers interfere with many analysis systems that include specific reagents that interact with the analysed target molecule. Such interference is often connected to certain buffer concentration.

Determination of the dissolution rate is carried out as follows: The TRIS buffer is sterilized at 122 °C before use. The SiO₂ concentration in the TRIS is kept below 30 ppm (to ensure *in sink* conditions; free dissolution of the SiO₂ matrix) during dissolution. The SiO₂ saturation level at pH 7.4 is about 150 ppm. When needed, a portion of the dissolution medium is changed to a fresh TRIS buffer in order to keep the SiO₂ concentration below 30 ppm. The dissolution rate is measured from the linear phase of the release curve that is typical after a typical initial deviation (slower or faster phase of release than the linear main part of the release) and before a typical slower phase of the release before the total 100 % SiO₂ dissolution. The linear phase of the release is typically longer than the deviating

phases in the beginning or in the end release. The linear phase of the release curve (wt-% dissolved SiO_2/h) can be defined by making a linear regression analysis of the measured release points (wt-% dissolved SiO_2/h). Points of a possible initial deviation phase (slower or faster phase of release than the linear main part of the release) are excluded if the points decrease the linear regression correlation factor (r^2) to be < 0.9 . The linear phase of the release curve (wt-% dissolved SiO_2/h) can be defined by making a linear regression analysis of measured release points (wt-% dissolved SiO_2/h) with a linear regression correlation factor ≥ 0.9 . The total amount (100 wt-%) of SiO_2 is calculated from the theoretical amount of SiO_2 that can be obtained from the sol composition according to the net reaction (e.g., 1 mol of used alkoxide, TEOS corresponds to 1 mol SiO_2).

The term *cell* means any living or dead cell of any organism. Thus cells of e.g. any animal, such as a mammal including a human, plant, bacteria and fungi are included.

The term *coating* refers to in the context of this application any coat with a thickness of < 0.5 mm on any surface.

Features of the invention

The present invention relates generally to biocompatible and bioresorbable sol-gel derived SiO_2 useful e.g. for drug delivery matrices, in tissue engineering, regenerative medicine and cell therapy in the living tissue or in contact with other living organisms, e.g. plants. The use of sol-gel derived SiO_2 can e.g. be oral, buccal, rectal, parenteral (e.g. subcutaneous injection, intramuscular injection, intravenous injection and intra-arterial injection), pulmonary, nasal, ocular, intrauterine, vaginal, urethral, topical, transdermal and surgically implantable delivery of monoliths, coatings, or nano- or microparticles as such or in suspension. The bioresorption of the SiO_2 matrices can be controlled by simple adjustments of the precursor ratios that influence condensation and aggregation of hydrolysed silica species. The bioresorbable matrices obtainable by this

invention can be applied for releasing different types of biologically active agents in a controlled manner dependent on the SiO_2 matrix bioresorption.

The present invention provides methods to control the bioresorption of sol-gel derived SiO_2 . The control of bioresorption is based mainly on the precursor ratio
5 adjustments and specific process parameters that quench the reactions affecting the bioresorption. The adjustably bioresorbable matrices can be utilised in the controlled release of biologically active agents. The biologically active agent can be e.g. in the form of salt like selegiline hydrochloride or in the form of free acid (ibuprofen) or free base (miconazole) or a neutral compound. The biologically
10 active agent can be a peptide, e.g. levodopa, a protein also an enamel matrix derivative of a protein or a bone morphogenetic protein. An effective amount of a biologically active agent can be added to the reaction at any stage of the process. The dissolving SiO_2 matrix may also itself act as a biologically active agent, especially in bone, where the dissolved silica species are known to affect the
15 formation of new bone. The adjustably bioresorbable sol-gel derived SiO_2 can also be used in contact with other living organisms, e.g., in contact with cell walls of plants to enhance plants' performance, e.g. against diseases. The biologically active agent can further be an agent with a biological effect on any tissue, cell or organism as defined and exemplified earlier.

20 Sol-gel derived SiO_2 is a very suitable material to be used for controlled release. Its contact with a living tissue is good, i.e., it is non-toxic and biocompatible. The nature of the sol-gel process that starts from a sol in the liquid phase makes it easy to add biologically active agents and if desired, the temperature can be kept at $\leq 40^\circ\text{C}$ during the whole process and the pH can largely be adjusted. In
25 addition, amorphous SiO_2 is bioresorbable at pH 7.4 and 37°C . Amorphous SiO_2 can be prepared by several ways, e.g., by a conventional high temperature melting-cooling process to produce glasses, but the use of the sol-gel process in the preparation of amorphous SiO_2 provides the best possibilities to adjust bioresorption as well as preserve the biological activity of the encapsulated agent.
30 Bioresorption depends both on chemical structure (e.g., the number of free SiOH groups or degree of condensation) of the SiO_2 as well as on the pore structure.

The denser the gel structure is the more important is the size of the material with respect to the bioresorption. If, e.g. a SiO_2 monolith or a particle has a very large surface area, such as several hundreds m^2/g , it usually contains also a lot of nanosized pores, which means that grinding of the monoliths or particles to be smaller, e.g. from 1 cm to 50 μm , does not significantly increase the surface area, only the diffusion path length becomes shorter. In the case of a dense SiO_2 monolith or a particle, both surface area and diffusion path length are strongly affected by grinding. Chemical and pore structure can be adjusted on a large scale by the sol-gel process. In addition to adjusting the precursor concentrations, the pore structure is commonly adjusted using additional organic templates (e.g., mesoporous MCM-41-type SiO_2), but most of the organic templates are not biocompatible and the pore structure can be adjusted well enough (with respect to the bioresorption) without any organic additives.

The mechanism of the release of a biologically active agent from the prepared SiO_2 may be diffusion or resorption controlled or a combination of both, but in any case, the role of bioresorption in the overall release rate of biologically active agents can be adjusted to be significant.

The present invention provides methods to prepare and adjust the bioresorption rates of SiO_2 on a large scale. This can be done by a alkoxy-based sol-gel or inorganic silicate method at conditions that can be adjusted to be friendly for several kinds of biologically active agents by adjusting the precursor ratios (water-to-alkoxide ratio, alcohol amount, pH), ageing of the sol and by using different preparation methods [e.g. ageing and gel formation and drying of the sol or the gel in a heat oven in normal atmosphere or in the 100 % or partial gas (e.g. N_2) atmosphere, or drying of the sol or gel by vacuum, electromagnetic energy, acoustic energy, spray-drying or freeze-drying]. The morphologies that can be prepared include monoliths (e.g. sticks, rods, tablets etc.), coatings, nano- and microspheres mainly for oral, buccal, rectal, parenteral, pulmonary, nasal, ocular, intrauterine, vaginal, urethral, topical, transdermal and surgically implantable administration or for tissue engineering, regenerative medicine and cell therapy. In addition, the amount of biologically active agent in the SiO_2 matrix, the biologically

active agent itself, ageing and drying temperature and the drying process conditions affect the bioresorption, but the main factor that controls the overall bioresorption rate is the ratio of precursors. It should also be noted that large amounts of the biologically active agent, protective agent for said biologically active agent or any additional substance of the sol comprised within the SiO₂ matrix increases dissolution of SiO₂, simply due to their presence making the SiO₂ structure more heterogenous.

The invention provides a specific narrow range of precursor ratios that result in fast dissolving SiO₂ structure and all deviations from this make the SiO₂ matrix dissolve slower in aqueous solutions at a pH from 7.0 to 7.5. In addition, the invention provides means to deviate from the chosen precursor ratios for a short time without losing the original effect of the original precursor ratios on the SiO₂ bioresorption.

The fastest dissolving SiO₂ matrices can be prepared, e.g. from alkoxides at conditions where the rate of hydrolysis is relatively fast, but the rate of condensation is at minimum, near a molar water to alkoxide (e.g. TEOS) ratio (R-value) of about 2 at a pH of about 2 and a high enough molar ratio of alcohol (e.g. EtOH) to alkoxide (e.g., TEOS) of about 1. These sols are formed, further aged and optionally also dried at low temperatures, preferably at $\leq 50^{\circ}\text{C}$, (low enough to preserve biological activity of an optionally comprised biologically active agent or agents) until a gel is formed. The gels can also aged and/or dried at low temperatures, preferably at $\leq 50^{\circ}\text{C}$. Alternatively, if no thermolabile biologically active agent is comprised high or even very high temperatures, up to e.g. 700°C , can be used.

Some methods of sol drying allow also short-time deviations from the chosen precursor ratio without losing the original effect of the original precursor ratio on the SiO₂ bioresorption. These methods lead to forced gel formation and practically stop or highly slow down, preferably quench all (e.g. condensation) reactions that affect the bioresorption rate (decreasing amount of SiOH during the condensation decreases the SiO₂ dissolution rate). The ageing time for the sol can be freely

chosen before the short-time affecting adjustments. Short time affecting adjustments can for example be an adjustment of pH to a pH from 5 to 7 and/or addition of water to decrease the relative amount of ethanol if required in order to maintain the biological activity of the ingredient. The ageing time affects the relative ratios of reacted silica species. After the desired ageing time of the sol, it is either spray or freeze dried so that the effect of deviations is short, preferably ≤ 5 minutes, but at least faster than ≤ 30 minutes. For microparticles made by spray-drying, deviation from the optimal fast-dissolving precursor ratio by diluting the sol with H_2O and/or alcohol, e.g. EtOH, makes it possible to prepare fast-dissolving microparticles. Spray-drying of the undiluted sol at high t/t_{gel} -values (≥ 0.9) is sometimes impossible due to its high viscosity.

Preferred embodiments

Typically an alkoxide, preferably tetraethoxysilane (TEOS), is used for preparing the sol-gel derived SiO_2 . If an inorganic silicate is used for preparing the sol-gel derived SiO_2 it is preferably sodium or potassium silicate. The lower alcohol is preferably ethanol.

If an induced change or changes of the composition of the sol is carried out, the change or changes are preferably selected from the group consisting of adding water, adding the alkoxide or inorganic silicate, adding the alcohol, adjusting pH by adding an acid or base, preferably the acid or base used as the catalyst, adding the optional bioactive agent or agents with or without protective agent or agents for said biologically active agent or agents affecting pH, molar ratio of water to the alkoxide or inorganic silicate, and/or molar ratio of alcohol to the alkoxide or inorganic silicate, and any combination thereof.

Drying of the sol can be drying by ambient heat, vacuum drying, electromagnetic drying, acoustic drying, spray-drying or freeze-drying, preferably spray-drying or freeze-drying. Forced drying of the sol can be carried out by spray-drying or freeze-drying. Freeze-drying can be initiated by freezing the sol.

The temperature of the sol is typically $\leq +90\text{ }^{\circ}\text{C}$, preferably $\leq +50\text{ }^{\circ}\text{C}$, most preferably $\leq +40\text{ }^{\circ}\text{C}$.

5 The gel obtained can be dried. Drying of the gel is typically drying by ambient heat, vacuum drying, electromagnetic drying, acoustic drying, spray-drying or freeze-drying, preferably ambient heat or freeze-drying. The gel is typically dried at a temperature of $\leq 700\text{ }^{\circ}\text{C}$, preferably $\leq 50\text{ }^{\circ}\text{C}$, and most preferably $\leq 40\text{ }^{\circ}\text{C}$.

10 A value that can be deviated to obtain a slower bioresorption rate is the ratio of water to the alkoxide or inorganic silicate, and the more the ratio of water to alkoxide or inorganic silicate is deviated to be higher or lower the slower the bioresorption rate obtained. Another value that can be deviated to obtain a slower bioresorption rate is the ratio of alcohol to the alkoxide or inorganic silicate, and the more the ratio is deviated to be higher or lower the slower the bioresorption rate obtained. The ratio of alcohol to alkoxide can be deviated to be as low as zero, i.e. the sol would originally comprise no alcohol. A further parameter that can be deviated to obtain a slower bioresorption rate is the pH, and the more the pH is deviated to be higher or lower the slower the bioresorption rate obtained.

A great change in molar ratio of water to alkoxide, e.g. from 2 to 50 or even up to 100, by adding water would simultaneously make the sol more biocompatible, e.g. the alcohol concentration would become lower.

20 A biologically active agent or agents can be added to the sol before gel formation. The biologically active agent or agents can be any agent inducing a biological response in a living tissue, organ or organism as defined and exemplified above. Typical biologically active agents are selected from the group consisting of a drug, peptide, protein, hormone, growth factor, enzyme, polysaccharide, living or dead cells or viruses or parts thereof, plasmids, polynucleotides, water soluble ions, salts and any combination thereof.

The pH value, molar ratio value of water to the alkoxide or inorganic silicate, and/or molar ratio value of alcohol to the alkoxide or inorganic silicate can be

changed to deviate from the ranges with which the fastest bioresorption rate is obtained, after sol ageing but before gel formation and/or optional addition of said biologically active agent or agents if within ≤ 30 minutes, preferably ≤ 15 minutes and most preferably ≤ 5 minutes, from the change forced drying of the sol is carried out or initiated.

The sol-gel derived SiO_2 is typically a monolith, preferably with a minimum diameter of ≥ 0.5 mm; a coating, preferably with a thickness of < 0.5 mm; or a particle, preferably with a maximum diameter of ≤ 100 μm .

Preferred dissolution rates of SiO_2 depend on which applications the SiO_2 is intended for. For many applications, such as oral, buccal, rectal, pulmonary, transdermal and other parenteral applications, high dissolution rates are required.

Monoliths with a minimum diameter of ≥ 0.5 mm without a biologically active agent other than the SiO_2 itself typically have a dissolution rate of the SiO_2 in TRIS buffer at a temperature of $+37^\circ\text{C}$ and pH 7.4 that is ≥ 0.04 wt-%/h, preferably ≥ 0.07 wt-%/h and more preferably ≥ 0.15 wt-%/h.

Coatings with a thickness of < 0.5 mm and comprising no biologically active agent other than the SiO_2 itself or comprising at least one biologically active agent other than the SiO_2 itself typically have a dissolution rate of the SiO_2 in TRIS buffer at a temperature of $+37^\circ\text{C}$ and pH 7.4 that is ≥ 0.04 wt-%/h, preferably ≥ 0.07 wt-%/h and more preferably ≥ 0.15 wt-%/h.

Particles with a maximum diameter of ≤ 100 μm comprising no biologically active agent other than the SiO_2 itself typically have a dissolution rate of the SiO_2 in TRIS buffer at a temperature of $+37^\circ\text{C}$ and pH 7.4 that is ≥ 0.04 wt-%/h, preferably ≥ 0.07 wt-%/h and more preferably ≥ 0.15 wt-%/h. A particle with a maximum diameter of ≤ 100 μm comprising at least one biologically active agent other than the SiO_2 itself typically have a dissolution rate of the SiO_2 in TRIS buffer at a temperature of $+37^\circ\text{C}$ and pH 7.4 that is ≥ 0.5 wt-%/h.

For some purposes high, very high and extremely high dissolution rates are preferable. Especially preferred dissolution rates of the SiO_2 for the monoliths, coatings and/or particles can for these purposes be up to $\geq 0.30 \text{ wt-\%/h}$, $\geq 0.5 \text{ wt-\%/h}$, $\geq 1.0 \text{ wt-\%/h}$, $\geq 2.0 \text{ wt-\%/h}$, $\geq 4.0 \text{ wt-\%/h}$, $\geq 6.0 \text{ wt-\%/h}$, $\geq 8.0 \text{ wt-\%/h}$ and even $\geq 10.0 \text{ wt-\%/h}$ depending on the particular application. The fastest dissolution rates are preferable for e.g. oral preparations.

In other cases long term dissolution rates are required for instance for certain parenteral applications, tissue engineering and regenerating medicine applications.

- 10 A monolith with a minimum diameter of $\geq 0.5 \text{ mm}$ comprising no biologically active agent other than the SiO_2 itself can typically have a dissolution rate of the SiO_2 in a TRIS buffer at a temperature of $+37^\circ\text{C}$ and pH 7.4 that is from 0.001 to 0.15 wt-\%/h , preferably from 0.002 to 0.07 wt-\%/h , and more preferably from 0.006 to 0.05 wt-\%/h .
- 15 A monolith with a minimum diameter of $\geq 0.5 \text{ mm}$ comprising at least one biologically active agent other than the SiO_2 itself can typically have a dissolution rate of the SiO_2 in a TRIS buffer at a temperature of $+37^\circ\text{C}$ and pH 7.4 that is from 0.001 to 0.06 wt-\%/h , preferably from 0.002 to 0.05 wt-\%/h , and more preferably from 0.006 to 0.025 wt-\%/h .
- 20 A coating with a thickness of $< 0.5 \text{ mm}$ comprising no biologically active agent other than the SiO_2 itself or comprising at least one biologically active agent other than the SiO_2 itself can typically have a dissolution rate of the SiO_2 in TRIS buffer at a temperature of $+37^\circ\text{C}$ and pH 7.4 that is from 0.001 to 0.15 wt-\%/h , preferably from 0.002 to 0.07 wt-\%/h , and more preferably from 0.006 to 0.05 wt-\%/h .
- 25 A particle with a maximum diameter of $\leq 100 \mu\text{m}$ comprising no biologically active agent other than the SiO_2 itself can typically have a dissolution rate of the SiO_2 in

TRIS buffer at a temperature of +37 °C and pH 7.4 that is from 0.001 to 0.008, and preferably from 0.002 to 0.003 wt-%/h.

5 A particle with a maximum diameter of $\leq 100 \mu\text{m}$ comprising at least one biologically active agent other than the SiO_2 itself can typically have a dissolution rate of the SiO_2 in TRIS buffer at a temperature of +37 °C and pH 7.4 that is from 0.001 to 0.10 wt-%/h, preferably from 0.002 to 0.07 wt-%/h, and more preferably from 0.006 to 0.05 wt-%/h.

10 A bioresorbable sol-gel derived SiO_2 , obtainable according to the method of the invention comprising a biologically active agent other than the SiO_2 itself that is a peptide, protein or cell typically has a dissolution rate of the SiO_2 in TRIS buffer at a temperature of +37 °C and pH 7.4 that is ≥ 0.04 wt-%/h, preferably ≥ 0.07 wt-%/h and more preferably ≥ 0.15 wt-%/h. For some applications an even more preferable dissolution rate is ≥ 0.5 wt-%/h and even ≥ 4.0 wt-%/h. For other applications a typical dissolution rate can be from 0.001 to 0.15 wt-%/h, 15 preferably from 0.002 to 0.07 wt-%/h, and more preferably from 0.006 to 0.05 wt-%/h.

Examples

Example 1

20 Matrix dissolution was studied by immersing silica monoliths in 0.005 or 0.05 M TRIS buffer solution (pH 7.4, 37 °C) in *in sink* conditions ($\text{SiO}_2 < 30$ ppm). The TRIS buffer was sterilized at 121 °C before use. The dissolution studies were done in the shaking water bath. The Si concentration of the TRIS buffer at different time points was measured with a spectrophotometer (UV-1601, Shimadzu) analysing the molybdenum blue complex absorbance at 820 nm. The 25 dissolution of the matrix is presented as cumulative release of SiO_2 from the matrix. The total amount (100 %) of SiO_2 is calculated from the theoretical amount of SiO_2 that can be obtained from the sol composition according to the net reaction (1 mol of used alkoxide, TEOS corresponds to 1 mol SiO_2).

The dissolution of SiO₂ monolith matrices 1 to 4 of example 1 are presented in figure 1.

Matrix 1 (figure 1)

5 The initial sol concentration (mol ratio) and calculated pH were: H₂O/TEOS = 2, ethanol/TEOS = 1, pH 2 (HCl was used to adjust the pH). Hydrolysis of the sol was done at room temperature. The sol was aged and dried simultaneously at 40 °C for 65 hours. After ageing and drying the pH of the sol was raised with 0.5 M NaOH to 6.3. 200 ml of the sol was pipetted into the test-tube and sank into liquid nitrogen in order to freeze the samples. After that the samples were freeze dried in
10 vacuum. The calculated SiO₂ dissolution rate was 0.407 wt-%/h.

Matrix 2 (figure 1)

The initial H₂O/TEOS (mol ratio) and calculated pH were: H₂O/TEOS = 30, pH 2.8 (HCl was used to adjust the pH). Hydrolysis was done at room temperature. The pH of the sol was raised with 1 M NH₃ to 5.1. The sol was then pipetted into the
15 mould and aged for 1 hour in a closed system and after that the gel was aged and dried simultaneously at 40 °C. Drying of the gel occurred at 40 °C with free evaporation to constant weight. The calculated SiO₂ dissolution rate was 0.179 wt-%/h.

Matrix 3 (figure 1)

20 The initial concentration (mol ratio) and calculated pH were: H₂O/TEOS = 15, pH 2 (HCl was used to adjust the pH). Hydrolysis of the sol was done at room temperature. The sol was aged and dried at 40 °C for 42 hours. After that the sol was pipetted into the mould and aged for 29 h at 4 °C in the closed mold. Drying and ageing of the sol and gel occurred at 4 °C with free evaporation to constant
25 weight. The calculated SiO₂ dissolution rate was 0.131 wt-%/h.

Matrix 4 (figure 1)

The initial sol concentration (mol ratio) and calculated pH were: $\text{H}_2\text{O}/\text{TEOS} = 3$, pH 2 (HCl was used to adjust the pH). Hydrolysis was done at room temperature. The sol was pipetted in to the mould and aged at 40 °C for 145.5 h. Drying of the gel occurred at 40 °C with free evaporation to constant weigh. The calculated SiO_2 dissolution rate was 0.008 wt-%/h.

Example 2

Matrix dissolution was studied by immersing silica microspheres in 0.005 or 0.05 M TRIS buffer solution (pH 7.4, 37 °C) in *in sink* conditions ($\text{SiO}_2 < 30$ ppm). TRIS was sterilized at 121 °C before use. The dissolution studies were done in the shaking water bath. The Si concentration of the TRIS at different time points was measured with spectrophotometer (UV-1601, Shimadzu) analysing the molybdenum blue complex absorbance at 820 nm. The dissolution of the matrix is presented as cumulative release of SiO_2 from the matrix. The total amount (100 %) of SiO_2 is calculated from the theoretical amount of SiO_2 that can be obtained from the sol composition according to the net reaction (1 mol of used alkoxide, TEOS corresponds to 1 mol SiO_2).

The dissolution of SiO_2 monolith microspheres 1 and 2 of example 2 are presented in figure 2.

20 Microsphere 1 (figure 2)

The initial concentration (mol ratio) and calculated pH were: $\text{H}_2\text{O}/\text{TEOS} = 2$, pH 2, ethanol/TEOS = 1 (HCl was used to adjust the pH). Hydrolysis was done at room temperature. The sol was aged and dried simultaneously at 40 °C for 22 hours. After that water and ethanol was added into the sol changing the $\text{H}_2\text{O}/\text{TEOS}$ mol ratio to 15 and ethanol/TEOS to 5.3. After that pH of the sol was adjusted with 5 M NaOH to 6.9. Microspheres were prepared by spraying silica sol with a mini spray dryer (B-191, Büchi Labortechnik AG, Switzerland) within 15 minutes after water and ethanol addition and pH adjustment to 6.9. The following process parameters

were used: pump 16 %, aspirator 95 %, and flow 600 l/h. The temperature of the spray nozzle was 120 °C. The calculated SiO₂ dissolution rate was 2.70 wt-%/h.

Microsphere 2 (figure 2)

The initial concentration (mol ratio) and calculated pH were: H₂O/TEOS = 30, pH 2.8 (HCl was used to adjust the pH). Hydrolysis was done at room temperature. The pH of the sol was adjusted after the sol hydrolysis with 1 M NH₃ to 5. Microspheres were prepared by spraying silica sol with a mini spray dryer (B-191, Büchi Labortechnik AG, Switzerland) within 15 minutes after the pH adjustment to 5. The following process parameters were used: pump 16 %, aspirator 95 %, and flow 600 l/h. The temperature of the spray nozzle was 135 °C. The calculated SiO₂ dissolution rate was 0.026 wt-%/h.

Example 3

SiO₂ monoliths were prepared in the following way, the initial concentration (mol ratio) and calculated pH were: H₂O/TEOS = 3, pH 2 (HCl was used to adjust the pH). Hydrolysis was done at room temperature. Propranolol (drug) was added into the sol. The amount of propranolol was 5 weight-% of the theoretical SiO₂ amount in the sol (1 mol TEOS = 1 mol SiO₂). After the propranolol had dissolved the sol was pipetted into the mould and aged at 40 °C for 145.5 h. Drying of the gel occurred at 40 °C with free evaporation to the constant weight.

Matrix dissolution and propranolol release was studied by immersing silica monoliths in 0.005 M TRIS buffer solution (pH 7.4, 37 °C) in *in sink* conditions (SiO₂ < 30 ppm) and 0.005 M TRIS buffer solution (pH 7.4, 37 °C) saturated with SiO₂ (SiO₂ 120–130 ppm). TRIS was sterilized at 121 °C before use. The dissolution studies were done in a shaking water bath. In a SiO₂ saturated TRIS solution the SiO₂ concentration does not increase even if a dissoluble silica matrix is placed into the solution. The Si concentration of the TRIS buffer at different time points was measured with a spectrophotometer (UV-1601, Shimadzu) analysing the molybdenum blue complex absorbance at 820 nm. The dissolution of the matrix in TRIS is presented as cumulative release of SiO₂ matrix. The total

amount (100 %) of SiO_2 is calculated from the theoretical amount of SiO_2 that can be obtained from the sol composition according to the net reaction (1 mol of used alkoxide, TEOS corresponds to 1 mol SiO_2). No matrix dissolution was observed in SiO_2 saturated TRIS. In a SiO_2 saturated TRIS solution the SiO_2 concentration
5 does not increase even if a dissolving silica matrix is placed into the solution. The propranolol concentration is measured directly with spectrophotometer at a wavelength of 227 nm. The release of the propranolol in TRIS and in SiO_2 saturated TRIS is presented as cumulative release.

SiO_2 monolith dissolution in TRIS, and propranolol release in TRIS and in SiO_2
10 saturated TRIS are presented in figure 3.

Curve 1 (figure 3)

Cumulative release of propranolol in TRIS solution.

Curve 2 (figure 3)

Cumulative dissolution of SiO_2 in TRIS solution. The calculated SiO_2 dissolution
15 rate was 0.009 wt-%/h.

Curve 3 (figure 3)

Cumulative release of propranolol in SiO_2 saturated TRIS solution.

Example 4

SiO_2 microspheres were prepared in the following way, the initial concentration
20 (mol ratio) and calculated pH were: $\text{H}_2\text{O}/\text{TEOS} = 30$, pH 2.8 (HCl was used to adjust the pH). Hydrolysis was done at room temperature. Propranolol (drug) was added into the sol. The amount of propranolol was 5 weight-% of the theoretical SiO_2 amount in the sol (1 mol TEOS = 1 mol SiO_2). Microspheres were prepared by spraying silica sol, with a mini spray dryer (B-191, Büchi Labortechnik AG,
25 Switzerland) within 15 minutes after the adding of propranolol. The following process parameters were used: pump 16 %, aspirator 95 %, and flow 600 l/h. The temperature of the spray nozzle was 120 °C.

Matrix dissolution and propranolol release was studied by immersing silica microspheres in 0.005 M TRIS buffer solution (pH 7.4, 37 °C) in *in sink* conditions ($\text{SiO}_2 < 30\text{--}130$ ppm) and 0.005 M TRIS buffer solution (pH 7.4, 37 °C) saturated with SiO_2 (SiO_2 120–130 ppm). TRIS was sterilized at 121 °C before use.

- 5 Dissolution studies were done in a shaking water bath. In a SiO_2 saturated TRIS solution the SiO_2 concentration does not increase even if a dissolving silica matrix is placed into the solution. The Si concentration of the TRIS buffer at different time points was measured with a spectrophotometer (UV-1601, Shimadzu) analysing the molybdenum blue complex absorbance at 820 nm. The dissolution of the
- 10 matrix in TRIS is presented as cumulative dissolution of SiO_2 matrix. The total amount (100%) of SiO_2 is calculated from the theoretical amount of SiO_2 that can be obtained from the sol composition according to the net reaction (1 mol of used alkoxide, TEOS corresponds to 1 mol SiO_2). No matrix dissolution was observed in SiO_2 saturated TRIS. The propranolol concentration is measured directly with a
- 15 spectrophotometer at a wavelength of 227 nm. The release of the propranolol in TRIS and in SiO_2 saturated TRIS and SiO_2 microsphere dissolution are presented as cumulative release in figure 4.

Curve 1 (figure 4)

Cumulative release of propranolol in TRIS solution.

20 Curve 2 (figure 4)

Cumulative dissolution of SiO_2 in TRIS solution. The calculated SiO_2 dissolution rate was 0.016 wt-%/h.

Curve 3 (figure 4)

Cumulative release of propranolol in SiO_2 saturated TRIS solution.

25 **Example 5**

SiO_2 monoliths were prepared in the following way, the initial concentration (mol ratio) and calculated pH were: $\text{H}_2\text{O}/\text{TEOS} = 30$, pH 2 (HCl was used to adjust the pH). Hydrolysis was done at room temperature. The sol was aged and dried

simultaneously at 40 °C for 66 hours. After ageing and drying the pH of the sol was adjusted with NaOH to 6.2 and a BSA-water solution (protein) was added into the sol. The amount of BSA was 5 weight-% of the theoretical SiO₂ amount in the sol (1 mol TEOS = 1 mol SiO₂). The H₂O/TEOS mol ratio after adding the BSA-water solution was 34. The sol was pipetted into the mould and aged at 4 °C. Drying of the gel occurred at 4 °C with free evaporation to the constant weight.

Matrix dissolution and BSA release was studied by immersing silica monoliths in 0.005 M TRIS buffer solution (pH 7.4, 37 °C) in *in sink* conditions (SiO₂ < 30 ppm). TRIS was sterilized at 121 °C before use. Dissolution studies were done in a shaking water bath. Si concentration of the TRIS at different time points was measured with a spectrophotometer (UV-1601, Shimadzu) analysing the molybdenum blue complex absorbance at 820 nm. Dissolution of the matrix is presented as cumulative release of SiO₂. The total amount (100%) of SiO₂ is calculated from the theoretical amount of SiO₂ that can be obtained from the sol composition according to the net reaction (1 mol of used alkoxide, TEOS corresponds to 1 mol SiO₂). BSA concentration was analysed with the fluorescence method (Photo Technology International) with NanoOrange Kit (Molecular Probes).

SiO₂ monolith dissolution and BSA release are presented in figure 5.

Curve 1 (figure 5)

Cumulative release of BSA in TRIS solution.

Curve 2 (figure 5)

Cumulative dissolution of SiO₂ in TRIS solution. The calculated SiO₂ dissolution rate was 0.196 wt-%/h.

Example 6

SiO₂ monoliths are prepared in the following way, the initial concentration (mol ratio) and calculated pH were: H₂O/TEOS = 22, pH 2.8 (HCl was used to adjust the pH). Hydrolysis of the sol was done at room temperature. pH of the sol was

adjusted with 0.5 M NaOH to 5.2 and BSA-water solution (protein) was added into the sol. The amount of BSA was 7 weight-% of the theoretical SiO_2 amount in the sol ($1 \text{ mol TEOS} = 1 \text{ mol SiO}_2$). The $\text{H}_2\text{O/TEOS}$ mol ratio after adding the BSA was 30. The sol was pipetted into the mould and aged at 4°C for 96 h. Drying of the gel occurred at 4°C with free evaporation to constant weight.

BSA release was studied by immersing silica monoliths in 0.005 M TRIS buffer solution (pH 7.4, 37°C) in *in sink* conditions ($\text{SiO}_2 < 30 \text{ ppm}$) and 0.005 M TRIS buffer solution (pH 7.4, 37°C) saturated with SiO_2 (SiO_2 120–130 ppm). TRIS was sterilized at 121°C before use. The release studies were done in the shaking water bath. In SiO_2 saturated TRIS solution BSA release is not caused by the matrix dissolution. BSA concentration was measured directly with a spectrophotometer at the wavelength of 220 nm. The release of the BSA in TRIS and in SiO_2 saturated TRIS is presented as cumulative release.

Release of BSA in TRIS and in SiO_2 saturated TRIS is presented in figure 6.

Curve 1 (figure 6)

Cumulative release of BSA in TRIS solution.

Curve 2 (figure 6)

Cumulative release of BSA in SiO_2 saturated TRIS solution.

Example 7

SiO_2 microspheres are prepared in the following way, the initial concentration (mol ratio) and calculated pH were: $\text{H}_2\text{O/TEOS} = 22$, pH 2.8 (HCl was used to adjust the pH). Hydrolysis was done at room temperature. pH of the sol was adjusted with 0.5 M NaOH to 5.3 and the BSA-water solution was added into the sol. The amount of BSA was 5 weight-% of the theoretical SiO_2 amount in the sol ($1 \text{ mol TEOS} = 1 \text{ mol SiO}_2$). The $\text{H}_2\text{O/TEOS}$ mol ratio after adding the BSA-water solution was 30. Microspheres were prepared by spraying the silica sol with a mini spray dryer (B-191, Büchi Labortechnik AG, Switzerland) within in 15 minutes after pH adjustment to 5.3 and BSA addition. The following process parameters were

used: pump 16 %, aspirator 95 %, and flow 600 l/h. The temperature of the spray nozzle was 120 °C.

BSA release was studied by immersing silica microspheres in 0.005 M TRIS buffer solution (pH 7.4, 37 °C) in *in sink* conditions ($\text{SiO}_2 < 30$ ppm) and 0.005 M TRIS
5 buffer solution (pH 7.4, 37 °C) saturated with SiO_2 (SiO_2 120–130 ppm). TRIS was sterilized at 121 °C before use. The release studies were done in a shaking water bath. In the SiO_2 saturated TRIS solution BSA release is not caused by the matrix dissolution. BSA concentration was measured directly with spectrophotometer at the wavelength 220 nm. The release of the BSA in TRIS
10 and in SiO_2 saturated TRIS is presented as cumulative release.

Release of BSA in TRIS and in SiO_2 saturated TRIS is presented in figure 7.

Curve 1 (figure 7)

Cumulative release of BSA in TRIS solution.

Curve 2 (figure 7)

15 Cumulative release of BSA in SiO_2 saturated TRIS solution.

It will be appreciated that the methods of the present invention can be incorporated in the form of a variety of embodiments, only a few of which are disclosed herein. It will be apparent for the specialist in the field that other
20 embodiments exist and do not depart from the spirit of the invention. Thus, the described embodiments are illustrative and should not be construed as restrictive.

CLAIMS

1. A method for preparing a sol-gel derived SiO_2 with a very fast bioresorption rate, said SiO_2 optionally comprising a specific percentage or percentages of a biologically active agent or agents other than the SiO_2 itself with or without protective agent or agents for said biologically active agent or agents, wherein method a sol-gel derived SiO_2 is prepared from a sol comprising water, an alkoxide or inorganic silicate and a lower alcohol, i.e. an alcohol with ≤ 4 carbons, using a mineral acid or a base as a catalyst, preferably a mineral acid, and said sol is aged and dried **characterised** in that

- 10 a) in the sol the starting
- i) pH is from 0.05 to 2.5, preferably 1.5 to 2.5, most preferably 2.0,
 - ii) molar ratio of water to the alkoxide or inorganic silicate is 0.5 to 2.5; preferably 1.5 to 2.5,
 - 15 iii) molar ratio of alcohol to the alkoxide or inorganic silicate is ≥ 0.5 , preferably ≥ 1.0 ; and
- b) either,
- i) the sol is, without induced changes of sol composition,
 - let to gel spontaneously at a temperature of $\leq 25^\circ\text{C}$ or an elevated temperature of 65°C to 90°C , preferably at an elevated temperature of 65°C to 90°C , or
 - gelation of the sol is done by forced drying of the sol, or
 - 20 ii) a change or changes of sol composition are induced after sol ageing but before gel formation, said change or changes of sol composition optionally comprising addition of said biologically active agent or agents with or without said protective agent or agents, and
- 25 the ratio t/t_{gel} is ≥ 0.005 , preferably ≥ 0.1 , most preferably ≥ 0.9 , wherein
- t is the ageing time of the sol, i.e. time from preparation of said sol to the induced changes, and

t_{gel} is the time point where the sol would have turned to a gel without the induced changes; and

forced drying of the sol is carried out or initiated within a time of ≤ 30 minutes, preferably ≤ 15 minutes, most preferably ≤ 5 minutes, from said induced change or changes.

5

2. A method for adjusting the bioresorption rate of sol-gel derived SiO_2 , optionally comprising a specific percentage or percentages of a biologically active agent or agents other than the SiO_2 itself with or without protective agent or agents for said biologically active agent or agents, **characterised** in that a SiO_2 with the fastest bioresorption rate is obtained according to claim 1; and a SiO_2 with a slower bioresorption rate than the fastest bioresorption rate is obtained by

10

a) deviating in the sol any of the starting values:

i) pH,

ii) molar ratio of water to the alkoxide or inorganic silicate, and/or

15

iii) molar ratio of alcohol to the alkoxide or inorganic silicate;

from the values defined in a) i) – iii) of claim 1;

b) carrying out induced changes by addition of a component or components, including optional addition of the biologically active agent or agents with or without said protective agent or agents, said changes affecting any of the values i) – iii)

20

of a) of claim 1 or a) if applied by

i) not carrying out forced drying, or

ii) carrying out or initiating forced drying of the sol later than defined in b) ii) of claim 1; and/or

c) deviating the temperature for letting the sol gel spontaneously from the values defined in b) i) of claim 1.

25

3. The method according to claim 1 or 2 **characterised** in that an alkoxide, preferably tetraethoxysilane (TEOS), is used for preparing the sol-gel derived SiO_2 .

4. The method according to claim 1, 2 or 3 **characterised** in that that an inorganic silicate, preferably sodium or potassium silicate, is used for preparing the sol-gel derived SiO_2 .
5. The method according to any of claims 1 to 4 **characterised** in that the lower alcohol is ethanol.
6. The method according to any of claims 1 to 5 **characterised** in that the induced change is selected from the group consisting of adding water, adding the alkoxide or inorganic silicate, adding the alcohol, adjusting pH by adding an acid or base, preferably the acid or base used as the catalyst, adding the optional bioactive agent or agents with or without protective agent or agents for said biologically active agent or agents affecting any of the values i) – iii) of a) in claim 1 or a) of claim 2 if applied, and any combination thereof.
7. The method according to any of claims 1 to 6 **characterised** in that drying of the sol is drying by ambient heat, vacuum drying, electromagnetic drying, acoustic drying, spray-drying or freeze-drying, preferably spray-drying or freeze-drying.
8. The method according to any of claims 1 to 7 **characterised** in that forced drying of the sol is carried out, preferably by spray-drying or freeze-drying.
9. The method according to claim 8 **characterised** in that forced drying is freeze-drying initiated by freezing the sol.
10. The method according to claim 8 or 9 **characterised** in that the temperature of the sol is $\leq +90^\circ\text{C}$, preferably $\leq +50^\circ\text{C}$, most preferably $\leq +40^\circ\text{C}$.
11. The method according to any of claims 1 to 10 **characterised** in that the gel is dried.

12. The method according to claim 11 **characterised** in that drying of the gel is drying by ambient heat, vacuum drying, electromagnetic drying, acoustic drying, spray-drying or freeze-drying, preferably ambient heat or freeze-drying.

13. The method according to claim 11 or 12 **characterised** in that the gel is
5 dried at a temperature of $\leq 700^{\circ}\text{C}$, preferably $\leq 50^{\circ}\text{C}$, and most preferably $\leq 40^{\circ}\text{C}$.

14. The method according to any of claims 2 to 13 **characterised** in that a
value to be deviated to obtain a slower bioresorption rate is the ratio of water to
the alkoxide or inorganic silicate, and the more the ratio of water to alkoxide or
10 inorganic silicate is deviated to be higher or lower the slower the bioresorption rate
obtained.

15. The method according to any of claims 2 to 14 **characterised** in that a
value to be deviated to obtain a slower bioresorption rate is the ratio of alcohol to
the alkoxide or inorganic silicate, and the more the ratio is deviated to be higher or
15 lower the slower the bioresorption rate obtained.

16. The method according to any of claims 2 to 15 **characterised** in that a
value to be deviated to obtain a slower bioresorption rate is the pH, and the more
the pH is deviated to be higher or lower the slower the bioresorption rate obtained.

17. The method according to any of claims 1 to 16 **characterised** in that a
20 biologically active agent or agents is added to the sol before gel formation.

18. The method according to any of claims 1 to 17 **characterised** in that any of
the values pH, molar ratio of water to the alkoxide or inorganic silicate, and/or
molar ratio of alcohol to the alkoxide or inorganic silicate is changed to deviate
from the ranges defined in claim 1, a) i) – iii), after sol ageing but before gel
25 formation and/or optional addition of said biologically active agent or agents, and
within ≤ 30 minutes, preferably ≤ 15 minutes and most preferably ≤ 5 minutes
from the change forced drying of the sol is carried out or initiated.

19. The method according to any of claims 1 to 18 **characterised** in that the sol-gel derived SiO_2 is a monolith, preferably with a minimum diameter of ≥ 0.5 mm; a coating, preferably with a thickness of < 0.5 mm; or a particle, preferably with a maximum diameter of $\leq 100 \mu\text{m}$.
- 5 20. The method according to any of claims 1 to 19 **characterised** in that the biologically active agent or agents is selected from the group consisting of a drug, peptide, protein, hormone, growth factor, enzyme, polysaccharide, living or dead cells or viruses or parts thereof, plasmids, polynucleotides, water soluble ions, salts and any combination thereof.
- 10 21. A bioresorbable sol-gel derived SiO_2 , obtainable according to the method of any of claims 1 to 20, **characterised** in that
- a) the SiO_2 is a monolith with a minimum diameter of ≥ 0.5 mm,
 - b) the SiO_2 comprises no biologically active agent other than the SiO_2 itself.
- 15 22. The SiO_2 of claim 21 **characterised** in that the dissolution rate of the SiO_2 in TRIS buffer at a temperature of $+37^\circ\text{C}$ and pH 7.4 is $\geq 0.04 \text{ wt-\%/h}$, preferably $\geq 0.07 \text{ wt-\%/h}$ and more preferably $\geq 0.15 \text{ wt-\%/h}$.
23. A bioresorbable sol-gel derived SiO_2 , obtainable according to the method of any of claims 1 to 20, **characterised** in that
- a) the SiO_2 is a monolith with a minimum diameter of ≥ 0.5 mm,
 - 20 b) the SiO_2 comprises at least one biologically active agent other than the SiO_2 itself, and
 - c) the dissolution rate of the SiO_2 in a TRIS buffer at a temperature of $+37^\circ\text{C}$ and pH 7.4 is $\geq 0.35 \text{ wt-\%/h}$.
- 25 24. A bioresorbable sol-gel derived SiO_2 , obtainable according to the method of any of claims 1 to 20, **characterised** in that
- a) the SiO_2 is a coating with a thickness of < 0.5 mm,
 - b) the SiO_2 comprises no biologically active agent other than the SiO_2 itself.

25. A bioresorbable sol-gel derived SiO_2 , obtainable according to the method of any of claims 1 to 20, **characterised** in that

- a) the SiO_2 is a coating with a thickness of < 0.5 mm,
- b) the SiO_2 comprises at least one biologically active agent other than the SiO_2 itself.

26. The SiO_2 of claim 24 or 25 **characterised** in that the dissolution rate of the SiO_2 in TRIS buffer at a temperature of $+37^\circ\text{C}$ and pH 7.4 is ≥ 0.04 wt-%/h, preferably ≥ 0.07 wt-%/h and more preferably ≥ 0.15 wt-%/h.

27. A bioresorbable sol-gel derived SiO_2 , obtainable according to the method of any of claims 1 to 20 **characterised** in that

- a) the SiO_2 is a particle with a maximum diameter of ≤ 100 μm ,
- b) the SiO_2 comprises no biologically active agent other than the SiO_2 itself, and.
- c) the dissolution rate of the SiO_2 in TRIS buffer at a temperature of $+37^\circ\text{C}$ and pH 7.4 is ≥ 0.04 wt-%/h, preferably ≥ 0.07 wt-%/h and more preferably ≥ 0.15 wt-%/h.

28. A bioresorbable sol-gel derived SiO_2 , obtainable according to the method of any of claims 1 to 20 **characterised** in that

- a) the SiO_2 is a particle with a maximum diameter of ≤ 100 μm ,
- b) the SiO_2 comprises at least one biologically active agent other than the SiO_2 itself, and
- c) the dissolution rate of the SiO_2 in TRIS buffer at a temperature of $+37^\circ\text{C}$ and pH 7.4 is ≥ 0.5 wt-%/h.

29. The SiO_2 according to any of claims 22, 26 and 27, **characterised** in that the dissolution rate of the SiO_2 is ≥ 0.30 wt-%/h.

30. The SiO_2 according to claim 23 or 29, **characterised** in that the dissolution rate of the SiO_2 is ≥ 0.5 wt-%/h preferably ≥ 1.0 wt-%/h, more preferably ≥ 2.0 wt-%/h and most preferably ≥ 4.0 wt-%/h.

5 31. The SiO_2 according to claim 21 **characterised** in that the dissolution rate of the SiO_2 in a TRIS buffer at a temperature of $+37^\circ\text{C}$ and pH 7.4 is from 0.001 to 0.15 wt-%/h, preferably from 0.002 to 0.07 wt-%/h, and more preferably from 0.006 to 0.05 wt-%/h.

32. A bioresorbable sol-gel derived SiO_2 , obtainable according to the method of any of claims 1 to 20, **characterised** in that

- 10 a) the SiO_2 is a monolith with a minimum diameter of ≥ 0.5 mm,
b) the SiO_2 comprises at least one biologically active agent other than the SiO_2 itself, and
c) the dissolution rate of the SiO_2 in a TRIS buffer at a temperature of $+37^\circ\text{C}$ and pH 7.4 is from 0.001 to 0.06 wt-%/h, preferably from 0.002 to 0.05 wt-%/h, and from 0.006 to 0.025 wt-%/h.
15

33. The SiO_2 according to claim 24 or 25 **characterised** in that the dissolution rate of the SiO_2 in TRIS buffer at a temperature of $+37^\circ\text{C}$ and pH 7.4 is from 0.001 to 0.15 wt-%/h, preferably from 0.002 to 0.07 wt-%/h, and more preferably from 0.006 to 0.05 wt-%/h.

20 34. A bioresorbable sol-gel derived SiO_2 , obtainable according to the method of any of claims 1 to 20 **characterised** in that

- a) the SiO_2 is a particle with a maximum diameter of $\leq 100\ \mu\text{m}$,
b) the SiO_2 comprises no biologically active agent other than the SiO_2 itself, and
25 c) the dissolution rate of the SiO_2 in TRIS buffer at a temperature of $+37^\circ\text{C}$ and pH 7.4 is from 0.001 to 0.008, and preferably from 0.002 to 0.003 wt-%/h.

35. A bioresorbable sol-gel derived SiO_2 , obtainable according to the method of any of claims 1 to 20 **characterised** in that

- a) the SiO_2 is a particle with a maximum diameter of $\leq 100 \mu\text{m}$,
- b) the SiO_2 comprises at least one biologically active agent other than the SiO_2 itself, and
- c) the dissolution rate of the SiO_2 in TRIS buffer at a temperature of $+37^\circ\text{C}$ and pH 7.4 is from 0.001 to 0.10 wt-%/h, preferably from 0.002 to 0.07 wt-%/h, and more preferably from 0.006 to 0.05 wt-%/h.

36. A bioresorbable sol-gel derived SiO_2 , obtainable according to the method of any of claims 1 to 20, **characterised** in that said SiO_2 comprises a biologically active agent other than the SiO_2 itself and said biologically active agent is a peptide or protein.

37. A bioresorbable sol-gel derived SiO_2 , obtainable according to the method of any of claims 1 to 20, **characterised** in that said SiO_2 comprises a biologically active agent other than the SiO_2 itself and said biologically active agent is a cell.

38. The SiO_2 of claim 36 or 37 **characterised** in that the dissolution rate of the SiO_2 in TRIS buffer at a temperature of $+37^\circ\text{C}$ and pH 7.4 is ≥ 0.04 wt-%/h, preferably ≥ 0.07 wt-%/h and more preferably ≥ 0.15 wt-%/h.

39. The SiO_2 according to claim 38, **characterised** in that the dissolution rate of the SiO_2 is ≥ 0.5 wt-%/h and preferably ≥ 4.0 wt-%/h.

40. The SiO_2 according to claim 36 or 37 **characterised** in that the dissolution rate of the SiO_2 in TRIS buffer at a temperature of $+37^\circ\text{C}$ and pH 7.4 is from 0.001 to 0.15 wt-%/h, preferably from 0.002 to 0.07 wt-%/h, and more preferably from 0.006 to 0.05 wt-%/h.

41. Use of a bioresorbable sol-gel derived SiO_2 obtainable according to the method of any of claims 1 to 20 for administering a biologically active agent to a human or animal body wherein said use comprises administering selected from

the group consisting of oral, buccal, rectal, parenteral, pulmonary, nasal, ocular, intrauterine, vaginal, urethral, topical and transdermal administering.

5 42. Use of a bioresorbable sol-gel derived SiO_2 according to any of claims 21 to 40 for administering a biologically active agent to a human or animal body, wherein said use comprises administering selected from the group consisting of oral, buccal, rectal, parenteral, pulmonary, nasal, ocular, intrauterine, vaginal, urethral, topical, transdermal and surgically implantable administering.

10 43. Use of a bioresorbable sol-gel derived SiO_2 obtainable according to the method of any of claims 1 to 20 for administering a biologically active agent to a plant.

44. Use of a bioresorbable sol-gel derived SiO_2 according to any of claims 21 to 40 for administering a biologically active agent to a plant.

ABSTRACT

The present invention relates to a method for preparing a sol-gel derived SiO_2 with a very fast bioresorption rate wherein a sol-gel derived SiO_2 is prepared from a sol comprising water, an alkoxide or inorganic silicate and a lower alcohol using a mineral acid or a base as a catalyst and said sol is aged and dried. Characteristic for the method is that pH is from 1.5 to 2.5, molar ratio of water to the alkoxide or inorganic silicate is 0.5 to 2.5, of alcohol to the alkoxide or inorganic silicate is ≥ 0.5 ; and the sol is either let to gel without induced changes of composition and without forced drying of the sol, or a change of composition are induced; and within a time of ≤ 30 minutes, from the induced change forced drying of the sol is carried out or initiated. The present invention also relates to a method for adjusting the bioresorption rate of sol-gel derived SiO_2 . Characteristic for the adjusting method is that a SiO_2 with the fastest bioresorption rate is obtained according to the method referred to above; and a SiO_2 with a slower bioresorption rate than the fastest bioresorption rate is obtained by deviating any of the parameters: pH, molar ratio of water to the alkoxide or inorganic silicate and/or molar ratio of alcohol to the alkoxide or inorganic silicate; carrying out induced changes by addition of a component or components and/or optional addition of the biologically active agent or agents, said changes affecting any of the values by not carrying out forced drying, or carrying out or initiating forced drying of the sol later; and/or deviating the temperature for letting the sol gel spontaneously. The invention further relates to bioresorbable sol-gel derived SiO_2 obtainable by the methods of the invention and to their use in administration of biologically active agents.

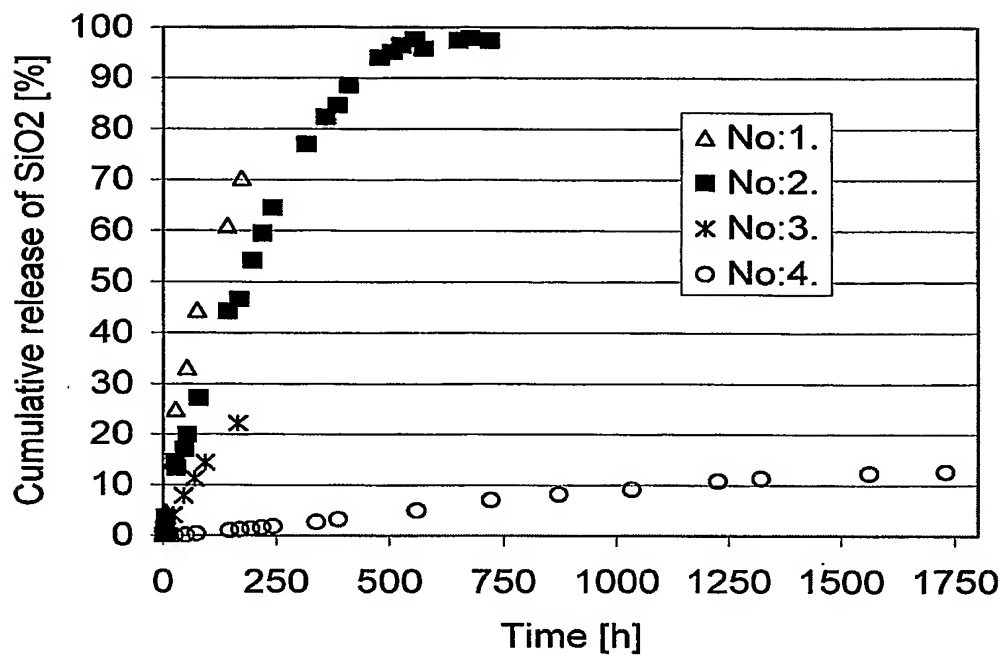


Figure 1

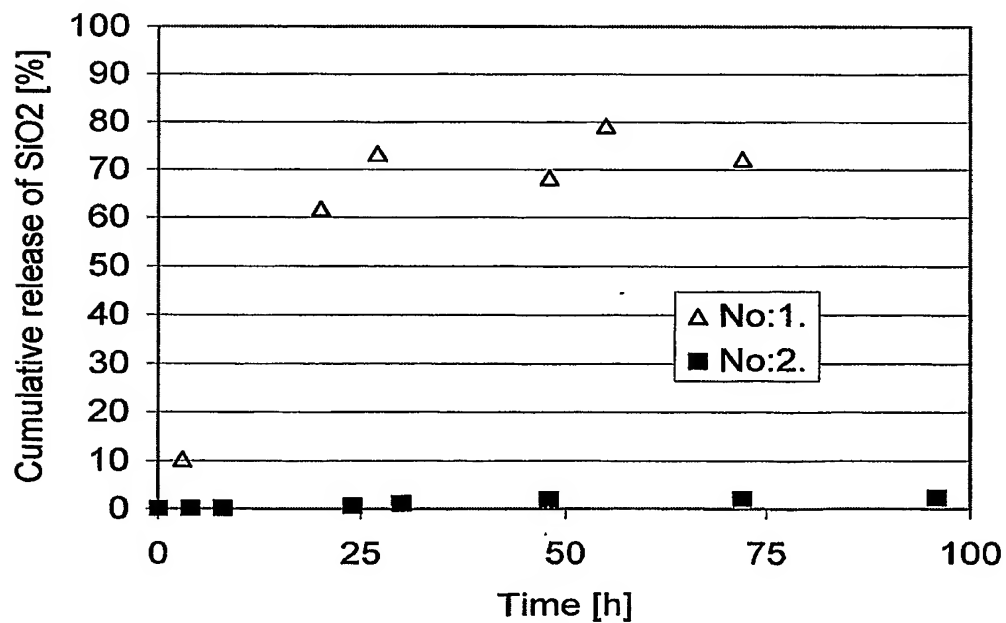


Figure 2

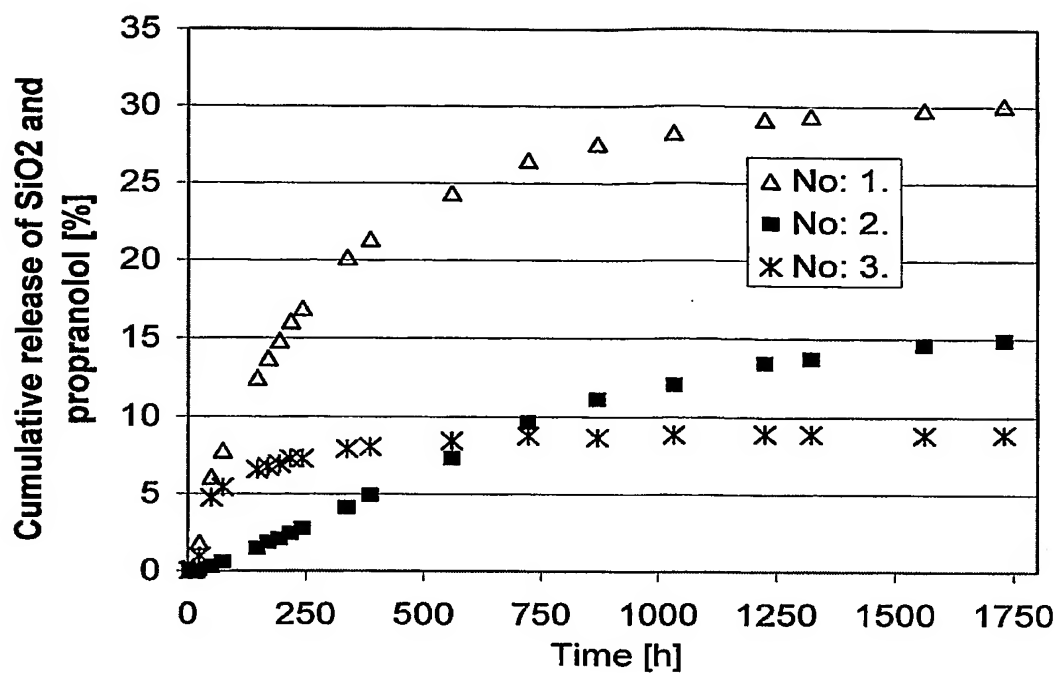


Figure 3

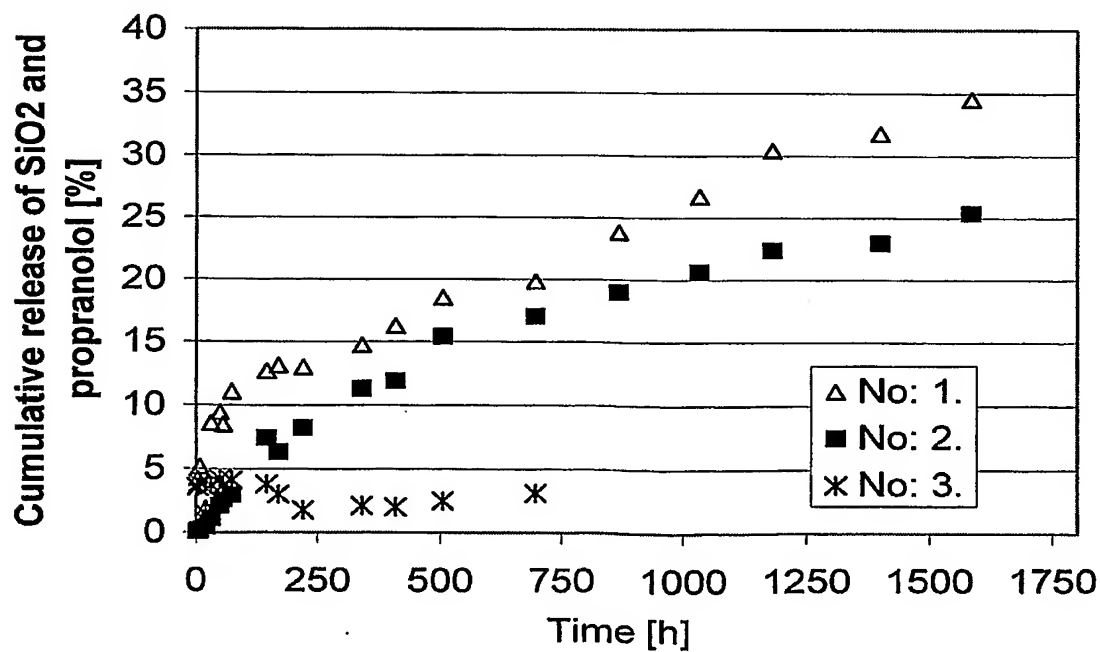


Figure 4

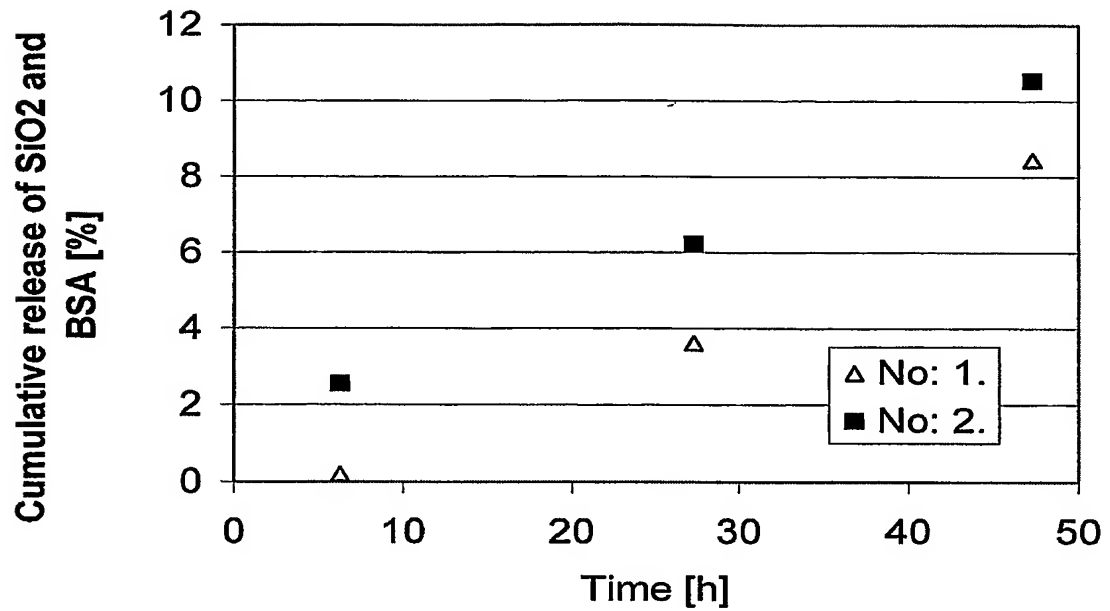


Figure 5

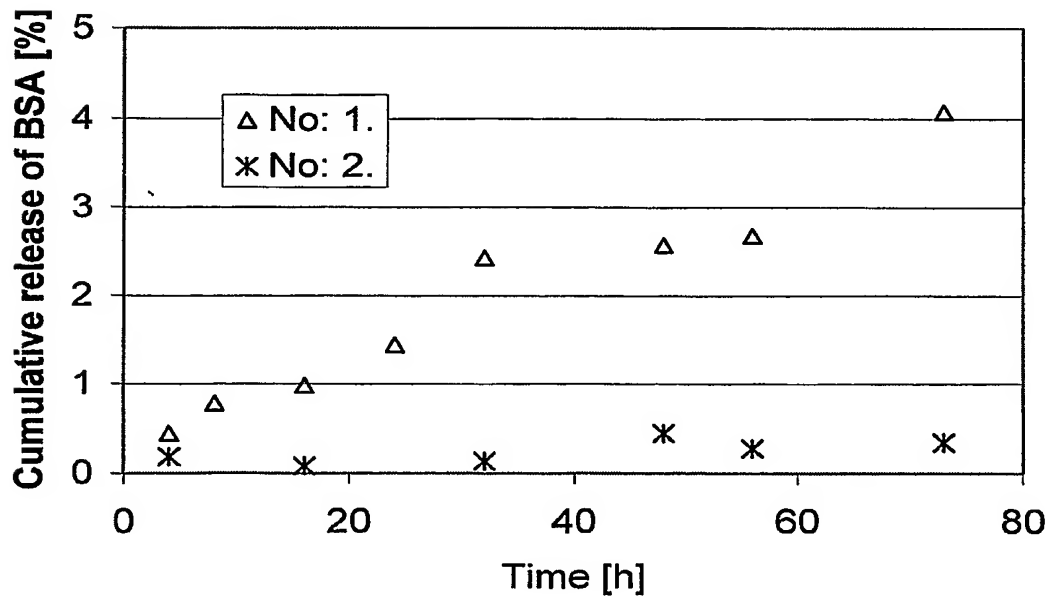
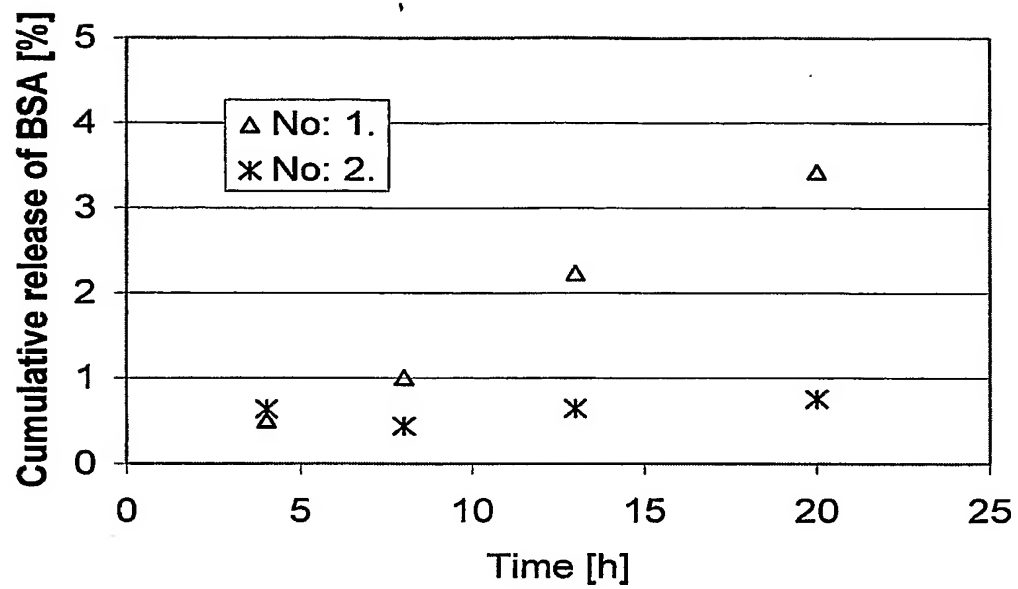


Figure 6

**Figure 7**